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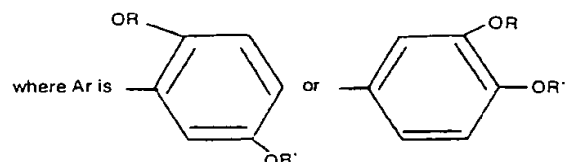
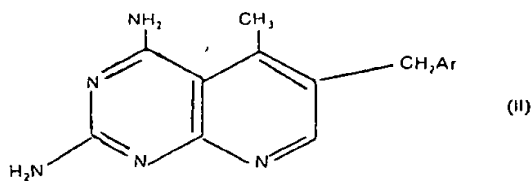
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54 Alkoxybenzylpyridopyrimidines, methods for their preparation, formulations thereof and their use in medicine.

57 Compounds of the formula (II):

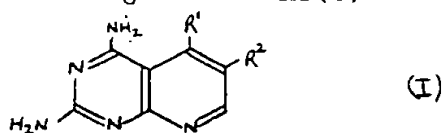


and R and R' are lower (C₁₋₆) alkyl and acid addition salts thereof, methods for the preparation thereof, formulations thereof and the use thereof as therapeutic agents, in particular as antiproliferative agents, are disclosed.



The present invention relates to 2,4-diaminopyrido(2,3-d)pyrimidines, to pharmaceutical formulations comprising such compounds and to their use in medicine.

U.K. patent No. 1 084 103 discloses 2,4-diaminopyrido(2,3-d)-
5 pyrimidines of the general formula (I)



in which R^1 is an alkyl group and R^2 is an unsubstituted benzyl group or a benzyl group substituted by one or more halogen atoms, alkyl or alkoxy groups.

The compounds of formula (I) were described as having high in vitro and in vivo activity against bacteria or bacterial infections in experimental
10 animals.

Subsequently it has been found that the compounds of formula (I) specifically disclosed in U.K. 1 084 103 show some inhibitory activity against mammalian dihydrofolate reductase (DHFR), and the activity was sufficient to render them potentially useful in the treatment of conditions
15 where inhibition of mammalian DHFR is desirable.

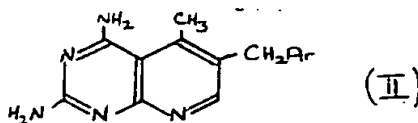
It has further been found that many of these compounds are potent inhibitors of histamine N-methyltransferase (HMT), an enzyme involved in the metabolism of histamine. In this manner they often cause an undesirable accumulation of histamine in organs and tissues. The effects of histamine
20 are well known and any possibility of a further utility for these compounds

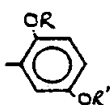
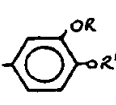
was substantially diminished by their strong inhibition of HMT.

Further investigation showed that a number of other compounds of formula (I) also posses DHFR inhibitory activity but that these, too, were also potent inhibitors of HMT. Others, which had acceptably low levels of inhibition of HMT were found to have insufficient activity as inhibitors of DHFR.

It has now been suprisingly found that certain 2,4-diamino-6-(dimethoxybenzyl)-5-methyl-pyrido(2,3-d)pyrimidines, which are within the scope of formula (I) but not specifically disclosed in U.K. 1 084 103, are not only very potent inhibitors of mammalian DHFR, but also have acceptably low inhibitory activity against HMT. These compounds are represented by formula (II) below and are useful in the treatment of proliferative diseases, such as psoriasis, basal and squamous cell carcinomas of the skin, and various forms of cancer including leukemias, lymphomas, sarcomas and solid tumors.

The invention accordingly provides compounds of formula (II):



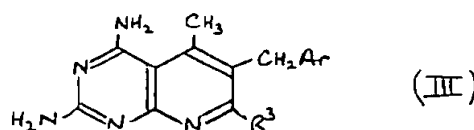
wherein Ar is  or  and R and R' are lower (C₁-C₆) alkyl; and pharmaceutically acceptable acid addition salts thereof. Preferably mono-basic salts are provided.

Preferably R and R' are methyl. Particularly preferred is 2,4-diamino-5-methyl-6-(2,5-dimethoxybenzyl)pyrido(2,3-d)pyrimidine.

The antiproliferative activity of the compounds of formula (II) resides in the free base and thus the nature of the acid participating in the acid addition salts is of minor importance. Such acid addition salts include, for example, those derived from hydrochloric acid, hydroiodic acid, sulphuric acid, phosphoric acid, acetic acid, p-toluenesulphonic acid, methanesulphonic acid, maleic acid, lactic acid, citric acid, tartaric acid, succinic acid, oxalic acid, p-chlorobenzenesulphonic acid, isethionic acid, glucuronic acid, pantothenic acid and lactobionic acid.

The compounds of formula (II) may be prepared by any method known in the art for the preparation of compounds of analogous structure.

In particular the compounds of formula (II) be prepared by the reductive cleavage of the corresponding 7-substituted compound of formula (III):



wherein Ar is as defined in formula (II) and R^3 is a leaving group capable of being removed by hydrogenolysis. Such groups include for example a mercapto or a halogeno (eg. chloro) group.

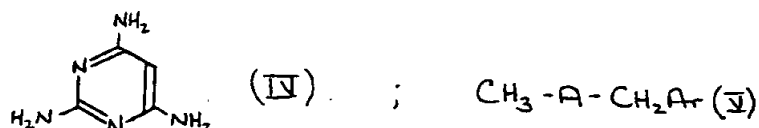
Where, in a compound of formula (III), R^3 is SH the dethiation may for instance be conveniently effected by reaction with a reducing agent, for example Raney nickel or Raney cobalt or by catalytic hydrogenation utilizing hydrogen in the presence of a catalyst such as palladium on charcoal.

Compounds of formula (III) wherein R^3 is a mercapto group may

be prepared from the corresponding 7-chloro compound (III) ($R^3 = Cl$) by
 reaction with a hydrosulfide as described in U.K. patent No. 913 710 or by
 treatment of the corresponding 7-hydroxy compound with phosphorus pentasulfide.

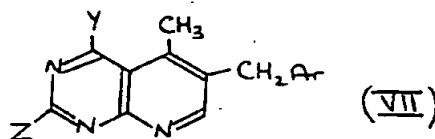
In the case where R^3 is a halogen atom in the compounds of formula
 (III), the compounds of formula (II) may for instance be conveniently obtained
 by e.g. catalytic hydrogenation.

The compounds of formula (II) may also be prepared by reacting
 2,4,6-triamino-pyrimidine (IV) with a compound of formula (V).



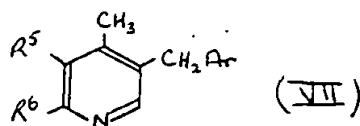
wherein Ar is as defined in formula (II);
 A is $\begin{matrix} -C- & C- \\ | & | \\ O & CHO \end{matrix}$, $R^4 = \begin{matrix} C= & C- \\ | & | \\ CHO & \end{matrix}$ or $\begin{matrix} O & CHR^4 \\ || & | \\ -C- & C- \end{matrix}$ and R^4 is a leaving group such as
 for example a tertiary amino, alkoxy, alkylthio, halogeno, sulphonate or
 tosylate group.

The compounds of formula (II) may additionally be prepared by
 the conversion to amino groups, by methods known in themselves in pyrimidine
 chemistry, of the hydroxy and/or mercapto group(s) in a compound of formula
 (VI):



in which Ar is as defined in formula (II), and Y and Z are the same or different and are OH, SH or NH₂ provided that at least one of Y and Z is OH or SH.

Compounds of formula (VI) maybe obtained by methods known in the art for preparing such compounds. In addition those in which Y is OH or NH₂ and Z is OH or SH may be obtained for example by reaction of urea, guanidine or thiourea with a suitable compound of formula (VII)



in which Ar is as defined in formula (II);

R⁵ is -CO₂H, CO₂ Alkyl, -CONH₂ or CN and

R⁶ is NH₂, Cl or Br.

While it is possible for the compounds of formula (II) or acid addition salts thereof (hereinafter referred to as the "active compounds") to be administered as the raw chemical they are preferably presented in the form of a pharmaceutical formulation.

The invention therefore further provides a pharmaceutical formulation comprising the active compound together with a pharmaceutically acceptable carrier therefor. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The invention additionally provides a method for the preparation

of a pharmaceutical formulation comprising bringing into association an active compound and a pharmaceutically acceptable carrier therefor.

Topical application is particularly suitable when the active compounds are for use in the treatment of proliferative skin diseases.

5 The term "topical" as applied herein relates to the use of the active ingredient incorporated in a suitable pharmaceutical carrier, and applied at the site of the disease for the exertion of local action.

Pharmaceutical formulations suitable for topical administration may be presented in anhydrous forms such as ointments, lotions, pastes,
10 jellies, sprays, aerosols, and bath oils. The term ointment includes formulations (including creams) having oleaginous, absorption, water soluble and emulsion type bases, for example petrolatum, lanolin, polyethylene glycols and mixtures thereof.

Topical formulations may contain a concentration of the active
15 ingredient of from 0.05 to 2% w/w preferably 0.1 to 1% w/w most preferably 0.2 to 0.5% w/w.

Other pharmaceutical formulations include those suitable for oral, rectal and parenteral administration, although of these oral is preferred. The formulations may, where appropriate, be conveniently presented in discrete
20 dosage units and may be prepared by any of the methods well known in the art of pharmacy. A convenient unit dose formulation contains the active compound in amount of from 50 mg to 1g, preferably 100mg to 500 mg, most preferably about 200 mg, to be taken once or several times daily.

All methods for the preparation of such formulations include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

5 Pharmaceutical formulations suitable for oral administration wherein the carrier is a solid are most preferably presented as unit dose formulations such as boluses, capsules, cachets or tablets each containing a predetermined amount of the active compound. A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed
10 tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding an inert liquid diluent. Tablets may be optionally coated and, if uncoated, may be optionally scored.
15 Capsules may be prepared by filling the active compound either alone or in admixture with one or more accessory ingredients, into the capsule cases and then sealing them in the usual manner. Cachets are analogous to capsules wherein the active ingredient together with any accessory ingredient(s) is sealed in a rice paper envelope.

20 Pharmaceutical formulations suitable for oral administration wherein the carrier is a liquid may be presented as a solution or a suspension in an aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

 Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories.
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Suitable carriers include cocoa butter and other material commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

5 Pharmaceutical formulations suitable for parenteral administration include sterile solutions or suspensions of the active compound in aqueous or oleaginous vehicles. Such preparations are conveniently presented in unit dosage or multi-dose containers which are sealed after introduction of the formulation until required for use.

10 It should be understood that in addition to the aforementioned carrier ingredients the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like, and substances
15= included for the purpose of rendering the formulation isotonic with the blood of the intended recipient.

 As has been described above the compounds of the present invention are useful for the treatment of proliferative diseases. The invention thus further provides a method for the treatment a of poliferative disease in a
20 mammal including man which comprises the administration of an effective, non-toxic amount of the active compound once or several times a day orally, or applied topically.

 The invention also provides a compound of formula (II) as herein-before defined or an acid addition salt thereof for use in medicine.

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The invention further provides a compound of formula (II) as
hereinbefore defined or an acid addition salt thereof for use in the treatment
of proliferative conditions.

5 The amount of active compound required for therapeutic effect
as an antiproliferative agent will of course vary not only with the particular
salt used but also with the route of administration. In general a suitable dose
for the treatment of a mammal (including man) will lie in the range of from
0.1 to 100 mg per kilogram bodyweight (mg / kg) per day, preferably in
the range of 2.0 to 50 mg / kg, more preferably in the range of 5 to 20 mg /kg.

10 Toxic manifestations attributable to the active compounds are
typically those associated with folate depletion, such as bone marrow depress-
ion, megaloblastic changes, and gastrointestinal ulceration. Calcium leucovorin
(calcium salt of 5-formyl-5,6,7,8,-tetrahydrofolic acid) may be administered
to effect reversal of these toxic manifestations or to prevent their occurrence.
15 The administration of calcium leucovorin may be effected concurrently with
treatment or at any stage thereof whenever toxic symptoms appear.

20 Thus, the haematological activity of the active compound can
be prevented or reduced by the simultaneous administration of leucovorin.
Consequently, tissue levels of the active compound may be safely raised
by increasing the dose of the compound together with a simultaneous adminis-
tration of leucovorin.

The following Examples, which illustrate the invention, and are
not intended as a limitation thereof.

EXAMPLE I 2,4-Diamino-5-methyl-6-(2,5-dimethoxybenzyl)pyrido-(2,3-d)pyrimidine

A mixture of 2,5-dimethoxybenzaldehyde (100 g), ethyl aceto-
acetate (84.5 g), anhydrous benzene (200 ml), piperidine (6 ml) and acetic
acid (12 ml) was heated at reflux for 3 hours in an apparatus fitted with
5 a Dean-Stark trap to collect the azeotropically distilled water. The reaction
mixture was cooled, benzene (300 ml) added and the solution washed successively
with water (100 ml), cold 0.1N hydrochloric acid (200 ml), 5% aqueous
sodium bicarbonate (200 ml) and dilute acetic acid (100 ml) and dried over
anhydrous magnesiumsulphate. The solvent was evaporated under reduced
10 pressure and the residual oil distilled, b.p. 169-170°C/0.3 mm Hg to give
ethyl α -(2,5-dimethoxybenzylidene)acetoacetate (104 g : 64%) which solidified
on standing (m.p. 68-69°C) was recrystallised from ethanol-pentane (mp.
72-73°C). A portion of the product (38g) was reduced catalytically in the
presence of 5% palladium on charcoal catalyst (Pd / C) in ethyl acetate
15 (150 ml). The product, after removal of solvent, was purified by distillation
under reduced pressure to give ethyl α -(2,5-dimethoxybenzyl)acetoacetate,
b. p. 146-148°C /0.3mm Hg.

A mixture of ethyl α -(2,5-dimethoxybenzyl)acetoacetate (21.2g),
2,4,6-triaminopyrimidine (10 g) and diphenyl ether (100 ml) was heated at
20 190-230°C for 1.5 hours in an apparatus fitted with a Dean-Stark trap and
water-ethanol (4 ml) was collected. Methanol (200 ml) and ethanol (50
ml) was added to the cooled reaction mixture. The resulting solid was collected
by filtration and treated with boiling water (1 l) to give 2,4-diamino-5-
methyl-6-(2,5-dimethoxybenzyl)-7-oxo-7,8-dihydropyrido(2,3-d)pyrimidine
25 (17 g) m.p. 325-326°C.

2,4-Diamino-5-methyl-6-(2,5-dimethoxybenzyl)-7-oxo-7,8-dihydropyrido(2,3-
d) pyrimidine (8 g) was chlorinated by treatment with Vilsmeier reagent
prepared by slowly adding thionyl chloride (28.6 g) in dry chloroform

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(25ml) to a solution of dimethylformamide (17.5 g) in chloroform (100 ml) at 0-5°C. The cold mixture of the pyridopyrimidine and Vilsmeier reagent was stirred, gradually allowed to reach ambient temperature and then heated at reflux for 3 hours. It was then treated with ethanolic base (80 ml), maintaining the temperature at 25-30°C with cooling. The brown product formed was isolated, treated further with aqueous ammonia and then recrystallised from ethanol to give 2,4-diamino-5-methyl-6-(2,5-dimethoxybenzyl)-7-chloropyrido(2,3-d)pyrimidine m.p. 193-196°C (dec.).

The chloro compound (0.3 g) was dissolved in ethanol (200 ml) containing potassium hydroxide (0.2g). 5% palladium on charcoal catalyst (0.2 g) was added and hydrogenation commenced. Reduction was complete after 48 hours and yielded 2,4-diamino-5-methyl-6-(2,5-dimethoxybenzyl)pyrido(2,3-d) pyrimidine, m.p. 252-254°C.

EXAMPLE 2 2,4-Diamino-6-(3,4-dimethoxybenzyl)-5-methylpyrido(2,3-d) pyrimidine

A mixture of 3,4-dimethoxybenzaldehyde (100 g), ethyl acetate (78 g) and anhydrous benzene (100 ml) was heated at reflux for 3 hours, during which time the theoretical amount of water was removed by azeotropic distillation. The solvent was then removed under reduced pressure and the residue recrystallised from ethyl acetate/pentane to give ethyl- α -(3,4-dimethoxybenzylidene)acetoacetate (153 g) m.p. 72°C. (analytical sample from additional recrystallization (ethanol-pentane), m.p. 85-86°C.)

Ethyl- α -(3,4-dimethoxybenzylidene)acetoacetate (50 g) was catalytically reduced in a Parr low pressure apparatus in ethyl acetate (150 ml) in the presence of 5% palladium on charcoal catalyst (Pd/C) (3 g). The catalyst

was removed by filtration, the solvent was removed under reduced pressure and the residual oil was distilled to give ethyl α -(3,4-dimethoxybenzyl)acetoacetate (42 g ; b.p. 162-164°C/0.4mm Hg).

A mixture of ethyl α -(3,4-dimethoxybenzyl)acetoacetate (42 g) and 2,3,6-triaminopyrimidine (21 g) in diphenyl ether (120 ml) was heated at 190-230°C for 2 hours during which time the ethanol and water formed were azeotropically removed. The reaction mixture was cooled and methanol (250 ml) and ethanol (50 ml) were added. The resulting solid was collected by filtration and treated with boiling water (1 l) to give 2,4-diamino-5-methyl-6-(3,4-dimethoxybenzyl)-7-oxo-7,8-dihydro-pyrido(2,3-d)pyrimidine (26 g), m.p. 346-348°C.

To a solution of dimethylformamide (17.5g) in chloroform (75 ml) was added thionyl chloride (14 g) in chloroform (25 ml) at 0-5°C. The reaction mixture was allowed to heat to 55-60° for about 5 minutes and cooled to 0°C. To the reaction mixture was added over a 20 minute period at 0°C 2,4-diamino-5-methyl-6-(3,4-dimethoxybenzyl)-7-oxo-7,8-dihydropyrido(2,3-d)pyrimidine (8.2 g). Chloroform (50 ml) was added and the mixture was heated at reflux for 2.5 hours, cooled and ethanolic base (50 ml) was added. The resulting brown product was collected by filtration, treated with 2N sodium hydroxide and recrystallized from ethanol to give crude product (7.6g). Additional recrystallisation from ethanol-water gave 2,4-diamino-5-methyl-6-(3,4-dimethoxybenzyl)-7-chloro-pyrido(2,3-d)pyrimidine (2 g) mp. 224-225°C (dec). This was added to ethanol (250 ml) containing potassium hydroxide (0.2g). 5% palladium on charcoal catalyst (0.1 g) was added and hydrogenation commenced. Reduction was complete after 4 hours in a Parrlow pressure apparatus at 35-40 psi and gave 2,4-diamino-6-(3,4-dimethoxybenzyl)-5-methyl-pyrido(2,3-d)pyrimidine (0.1g), m.p. 265-268°C (dec).

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EXAMPLE 3 Inhibition of Mammalian Dihydrofolate Reductase DHFR by
2,4-Diamino-6-benzylpyrido(2,3-d)pyrimidines

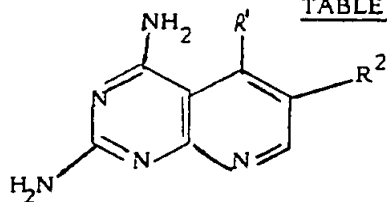
The inhibitory effect of the test compounds against DHFR partially purified from rat liver was determined. The results are given in Table 1 below.

5 An IC_{50} of $5 \times 10^{-8}M$ or less is considered significant potency, an IC_{50} of $1 \times 10^{-8}M$ or less being particularly significant potency.

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TABLE 1



TEST COMPOUND		IC ₅₀ 10 ⁸ M
R ¹	R ²	
CH ₃	-CH ₂ Ph	4
CH ₃		1.6
CH ₃		2.7
CH ₃		5.0
CH ₃		5.3
CH ₃		9
H		25
CH ₃		0.15
CH ₃		0.78

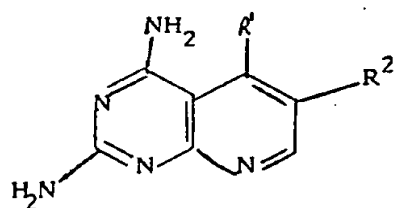
EXAMPLE 4 Inhibition of Histamine N-methyl-transferase (HMT) by 2,4-Diamino-6-benzylpyrido(2,3-d)pyrimidine

5 The effect of the test compounds used in Example 3 against HMT was determined. The results are given in Table 2. An inhibition of less than 20% was considered acceptable and the lack of any effect on this enzyme is most desirable since any interference with histamine metabolism should be minimized.

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TABLE 2

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TEST COMPOUND		% inhibition of HMT at $10^{-5}M$
R^1	R^2	
CH_3	$-CH_2 Ph$	51
CH_3		59
CH_3		Not Tested
CH_3		18
CH_3		20
CH_3		55
H		48
CH_3		11
CH_3		19

EXAMPLE 5 Antitumor effect of 2,4-diamino-6-(2,5-dimethoxy-benzyl)-5-methylpyrido(2,3-d)pyrimidine

Solid Walker 256 tumors were implanted subcutaneously into three groups of rats. On the third day after implantation with the tumors drug treatment was commenced and continued for 5 successive days. One group of rats was treated with 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido(2,3-d) pyrimidine at a dose of 25mg/kg q.i.d., a second group was treated with the same compound at 15 mg/kg b.i.d.; the third group were left untreated as controls. After 17 days the treated groups of rats showed mean tumor volumes of 29% and 10% respectively of the untreated group.

In a second study tumors were implanted subcutaneously and drug treatment delayed until 10 days after implantation. Drug treatment consisted of 30 mg/kg q.i.d. on days 10-13 and 50 mg/kg on days 20, 24 and 28 after tumor implantation. Mean tumor volumes were measured during the course of this study. Tumor volume in animals which received no treatment grew rapidly whereas those which received drug treatment showed a decrease in mean tumor volume during the period of observation. Twenty-three days after tumor implantation T/C was 0.03.

EXAMPLE 6 Antileukemic effect of 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido(2,3-d)pyrimidine

Leukemia P388 cells were inoculated intraperitoneally in CDF, Charles River female mice, each animal receiving 10^6 cells. On the second

day after implantation with the leukemic cells, drug treatment was commenced and continued twice daily for three days. Four groups of mice were treated with 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido(2,3-d)pyrimidine at doses of 22, 33.5, 50 and 75 mg/kg of body weight and a fifth group was left untreated as a control. All of the untreated mice died from the leukemia between the 10th and 12th day with a median survival of 11 days. All of the treated mice survived for periods longer than the untreated animals with a % increases in life span of 145%, 159%, 140% and 154% for the drug treated groups receiving 22, 33.5, 50 and 75 mg/kg doses respectively. This is a highly significant effect. There was no evidence of drug-related toxicity.

Within the same experiment, two closely related compounds were tested for antileukemic activity at the same dosage levels of 22, 33.5, 50 and 75 mg/kg, respectively, and with the same schedule of treatment. The corresponding pyridopyrimidine with a 4-methoxybenzyl substituent was inactive at all doses and the 2-chlorobenzyl compound had only marginal or slight activity. Thus, the 2,5-dimethoxybenzyl compound has substantially greater antileukemic activity than those compounds of similar structure.

EXAMPLE 7 Water Soluble Ointment

	<u>amount(g)</u>
2,4-Diamino-5-methyl-6-(dialkoxy- benzyl)pyrido(2,3-d)pyrimidine	0.5
Polyethylene glycol 300	20.0
Polyethylene glycol 1500	<u>77.5</u>
Total	100.0

EXAMPLE 8 Skin Cream

	<u>amount (g)</u>
2,4-Diamino-5-methyl-6-(dialkoxy-	
benzyl)pyrido(2,3-d)pyrimidine	0.5
Glyceryl monostearate	20.0
Methylparaben	0.3
5 Petrolatum light liquid	4.0
Propylene glycol	5.0
Span 60	2.0
Tween 61	4.0
Water	<u>64.2</u>
10 Total	100.0

EXAMPLE 9 Toxicity of 2,4-Diamino-5-methyl-6-(dimethoxybenzyl)pyrido(2,3-d)pyrimidines

The acute toxicity of the title compounds was determined in mice (i.p.). The following results were obtained:-

15 6-benzyl derivative	LD ₅₀ (mg/kg bodyweight)
2,5-dimethoxy	≈ 500

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EXAMPLE 10 TABLET FORMULATION

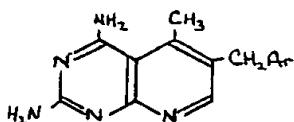
	2,4-Diamino-5-methyl-6(dialkoxybenzyl) pyrido(2,3-d)pyrimidine	100 mg
	Starch	50 mg
5	Lactose	50 mg
	Stearic acid	3 mg
	Gelatin	15 mg
	Total	<hr/> 218 mg

10 EXAMPLE 11 INJECTABLE FORMULATION

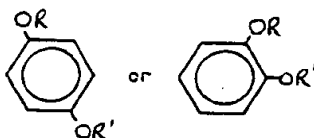
	2,4-Diamino-5-methyl-6- (dialkoxybenzyl)-pyrido(2,3-d)pyrimidine q.s. to	5mg/ml
	Propylene glycol	40ml
	Ethanol	11ml
15	Water	9ml

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1. A compound of the formula (II) :



wherein Ar is

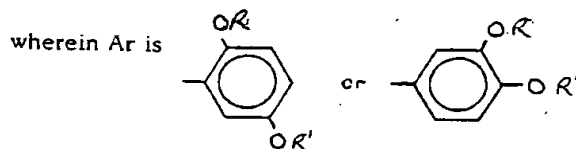
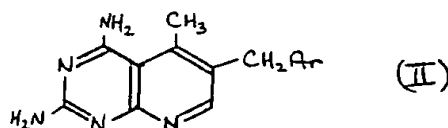


R and R' are lower (C_1-C_6) alkyl,

and acid addition salts thereof.

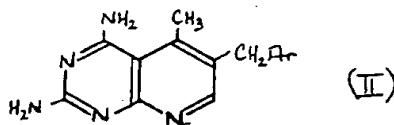
2. A compound of formula (II) as claimed in claim 1 wherein R and R' are methyl.
3. 2,4-Diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido(2,3-d)pyrimidine and acid addition salts thereof.
4. A pharmaceutical formulation comprising a compound of formula (II) and acid addition salts thereof, together with a pharmaceutically acceptable carrier therefor.
5. A pharmaceutical formulation as claimed in claim 4 in unit dosage form.

6. A pharmaceutical formulation as claimed in claim 5 wherein the pyridopyrimidine is present in an amount of from 50mg to 1g
7. A pharmaceutical formulation as claimed in claim 4 wherein the formulation is a topical formulation.
8. A pharmaceutical formulation as claimed in claim 7 wherein the pyridopyrimidine is present in an amount of 0.2% to 5% w/w.
9. A compound of formula (II):

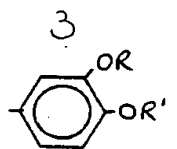
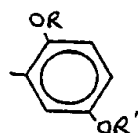


R and R' are lower (C₁-C₆) alkyl

- and acid addition salts thereof for use as a therapeutic agent.
10. A compound as claimed in claim 9 for use in the treatment or prophylaxis of proliferative diseases.
11. A method for the preparation of a compound of formula (II):



wherein Ar is



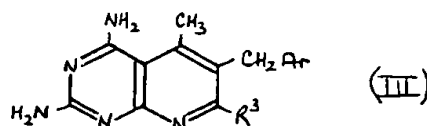
R and R' are lower (C₁-C₆) alkyl

and acid addition salts thereof,

which method comprises:-

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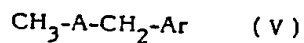
(A) reductive cleavage of a compound of formula (III)



wherein Ar is as defined in formula (II) and

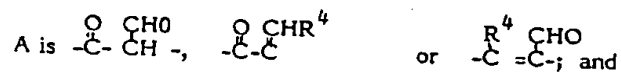
R³ is a leaving group capable of removal by hydrogenolysis;

(B) reacting 2,4,6-triaminopyrimidine with a compound of formula (V)



10

wherein Ar is as defined in formula (II);

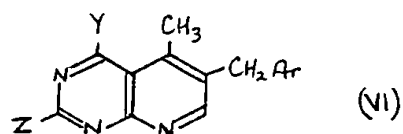


R⁴ is a leaving group; or

(C) Conversion to amino groups of the hydroxy and / or mercapto

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groups in a compound of formula (VI)



wherein Y and Z are the same or different and are OH, SH or NH_2 provided that at least one of Y and Z is OH, or SH; and Ar is as defined in formula (II);



European Patent
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EUROPEAN SEARCH REPORT

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Application number

EP 80 10 3325.9

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D, X	<u>GB - A - 1 084 103</u> (WELLCOME FOUNDATION) * claims 1, 8, 10 * --	1, 4, 5, 11	C 07 D 471/04 A 61 K 31/505 /(C 07 D 471/04, 239/00, 221/00)
D	<u>GB - A - 913 710</u> (WELLCOME FOUNDATION) * claims 4, 5 * --	4, 5, 11	
	<u>GB - A - 970 583</u> (WELLCOME FOUNDATION) * claim 4 * --	1	
	<u>US - A - 3 322 765</u> (G.H. HITCHINGS et al.) * claim 1 * ----	1	TECHNICAL FIELDS SEARCHED (Int. Cl.) A 61 K 31/505 C 07 D 471/04
			CATEGORY OF CITED DOCUMENTS X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
<input checked="" type="checkbox"/> The present search report has been drawn up for all claims			&: member of the same patent family, corresponding document
Place of search Berlin		Date of completion of the search 29-09-1980	Examiner FROELICH